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REMARKS

Claims 1, 2, 14-20 and 26-32 are pending in the application. Claims 3-13, 21-25 and 33-38 have been withdrawn.

Specification

Applicant wish to point out to the Examiner that page 7, 8 and 10 of the description were amended to identify the terms "ON", "PS-ODN" and "PO-ODN" with their complete names as requested by the Examiner. The words "phosphorothioate", "selected abbreviations", "spectrum", "requirement" and "sequence" were corrected on pages 8, 33, 36, 37 and 50. The word "oligonucleotides" was also corrected on page 52 of the description. The Applicant wish to respectfully point out that the errors alleged by the Examiner were corrected despite the fact that the subtitles on pages 33, 36, 37, 50 and 52 in our files had no typographical errors. No new matter is being hereby introduced.

Further, the Examiner alleges that the specification is objected to for failing to adhere to the requirements of the sequence rules. The Applicants wish to respectfully point out that an amendment in response to a notice under 37 CFR §§1.821-825 was filed on April 12, 2004. The specification, in particular Table I, was amended to append SEQ ID NOs to all mentions of specific sequences. In addition, it is believed that the sequence listing submitted previously complies with Rule 37 CFR §§ 1.821(a-h). Examiner will find enclosed with the present Response a copy of such amendment. It is believed that the Examiner rejection is moot.

Information Disclosure Statement

In addition, the Applicants wish to respectfully point out that an Information disclosure statement has been filed on May 4, 2006, previously to the submission of the present response.

Double Patenting

Claims 1, 2, 14-20 and 26-32 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5, 7-10, 12-14, 18-20, 28 and 29 of copending Application No 11/661,403. In order to overcome this

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rejection, enclosed herewith is a Terminal Disclaimer under 37 C.F.R. §1.321. It is believed that with such a Terminal Disclaimer on file, rejection under double-patenting is moot.

Claim rejections - 35 U.S.C. § 112

Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph. The Examiner argues that there is insufficient antecedent for the expression "said anti-HIV activity" in the second last sentence of claim 1. The Applicants wish to respectfully point out that claim 1 was amended to include the expression "said oligonucleotide have an anti-HIV activity". Reconsideration of the Examiner's rejections is respectfully requested.

Claims 1, 2, 14-20 and 26-32 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner mentions that the specification, while being enabling for *in vitro* inhibition of part of the HIV life cycle in cell culture, does not reasonably provide enablement for the prophylaxis or treatment of a HIV infection *in vivo*, especially if the subject is a human. The Examiner also argues that given the divergence of *in vitro* and *in vivo* HIV-1 specific immune responses, the clinical relevance in the art would be burdened with an undue quantity of *in vivo* experiments in order to make and use the current invention since the Applicants have not provided any clear-cut evidence to demonstrate that the claimed oligonucleotides can prevent or treat HIV infection when the subjects encompasses *in vivo* application. Absent working examples and specific teachings of the clinical efficacy, therapeutic index, and pharmacokinetic properties of the oligonucleotides, those in the art would not be able to use the claimed method for the prophylaxis or treatment of HIV infection with the oligonucleotides claimed in the present invention. In order to overcome this rejection, the Applicants wish to respectfully argue that the USPTO is not entitled to substitute itself to the FDA in order to evaluate the clinical relevance of the present invention. In addition, it is believed that the present invention has clinical relevance and that the *in vitro* results disclosed in the present application do not diverge from *in vivo* responses. To

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support this latter allegation, enclosed is a Declaration from Dr. Jean-Marc Juteau, one of the inventors, reporting *in vivo* results obtained with a Simian Immunodeficiency Virus (SIV) model showing the anti-retroviral activity of sequence independent oligonucleotides of the present invention in non-human primates. In addition, results are also presented demonstrating the anti-retroviral activity of the sequence independent oligonucleotides of the present invention in a Friend Leukemia Virus model. The *in vivo* SIV model is the only model available unless Applicants initiate Clinical phase III trials. At the time being, the SIV model used in the present Declaration shows 98% identity with HIV-2, which is thus by far the best model to prove efficacy with.

In view of the foregoing, reconsideration and withdrawal of the Examiner's rejection of claims 1, 2, 14-20 and 26-32 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claim rejections - 35 U.S.C. § 102

Claims 1, 14-17, 28 and 30-32 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Andreola *et al.* The Examiner alleges that the document of Andreola *et al.* teaches a plurality of non-complementary anti-HIV random oligonucleotides that bind to the HIV component, RNase H. Two of the oligonucleotides are 81 nucleotides long and have an IC_{50} of 30 nM for HIV infectivity in cell culture. The Applicants wish to argue that, contrary to the present invention, Andreola *et al.* teaches identification of oligonucleotides having an antiviral activity due to their sequence. Further, Andreola *et al.* discloses a screening of a library of oligonucleotides corresponding to 4^{35} possible sequences using the SELEX procedures. By this technique, they identified oligonucleotides having high affinity to RNAse H domain of HIV-1 RT. As described in page 10090 (first column, last paragraph) in Andreola *et al.*, some selected

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oligodeoxynucleotides are inhibitors of RNAse H activity while other are not. In consequence, the oligodeoxynucleotides need to have high affinity to RNAse H domain of HIV-1 RT to inhibit RNAse H activity. This demonstrates that the activity is sequence dependent. Moreover, in page 10091 (first column, first paragraph), the HIV-1 room temperature activity can be removed from an active selected oligodeoxynucleotide by substituting residues. This demonstrates again that the activity is sequence dependent. Finally, in a cellular antiviral assays, Fig. 7 in Andreola *et al.* shows that two selected oligodeoxynucleotide are active while two other are non active, demonstrating the sequence dependent antiviral activity. The present invention is claiming oligonucleotides having an anti-HIV activity wherein said activity occurs principally by a sequence independent mode of action. Consequently, claim 1 was amended to clearly encompass that anti-HIV activity occurs principally by a sequence independent mode of action. Support can be found on page 13 of the description, which was amended to clarify the intended definition of a non-sequence complementary mode of action. No new matter is being hereby introduced. In view of the arguments submitted hereinabove, reconsideration of the Examiner's rejections is respectfully requested.

Claim rejections - 35 U.S.C. § 103

Claims 1, 14-16, 18-20, 26 and 28-31 have been rejected under 35 U.S.C. § 103(a) as being obvious over Marshall *et al.* in view of Mergny *et al.* and Matsukura *et al.* The Examiner alleges that Marshall *et al.* teaches the method of inhibition of HIV activity by phosphorothioate oligodeoxycytidines, with an IC_{50} of 0.01 μM. These oligonucleotides bind to HIV reverse transcriptase and gp120 in a non-sequence-complementary manner. Marshall *et al.* does not teach an anti-HIV oligonucleotide long of 29 nucleotides but emphasizes that phosphorothioate

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oligomers of greater length are required for potent inhibition, as evidenced by the IC_{50} values disclosed. The Examiner also mentions that Mergny *et al.* teaches phosphorothioate-linked cytosine-rich 29-mers, which form a tetrad of two duplexes "zipped together" in an anti-parallel fashion, have high stability as compared to shorter oligomers. Finally, the Examiner alleges that Matsukura *et al.* teaches randomers derived from *art/trs* region in the HIV genome and suggest combining a phosphorothioate oligodeoxicitidines with different HIV inhibitor to enhance antiviral activity. Consequently, the Examiner alleged that it would have been *prima facie* obvious to one ordinary skill in the art to increase the length of the phosphorothioate oligonucleotides to 29 nucleotides for the purpose of increasing the potency of anti-HIV oligonucleotides, thus rendering obvious the present invention. The Applicants disagree and would like to respectfully argue that, as mentioned by the Examiner, Marshall *et al.* does not teach any randomer oligonucleotide, more specifically an oligonucleotide of at least 30 nucleotides, as now claimed in claim 1 of the present invention, with an anti-HIV activity wherein said activity occurs principally by a sequence independent mode of action. The Applicants also would like to point out that the document of Marshall *et al.* teaches that an oligodeoxicitidines of 14 nucleotides in length have the same efficacy in inhibiting an HIV infection than an oligodeoxicitidines of 28 nucleotides in length. Thus, since shorter oligonucleotides can be transported more easily through cellular membrane and since shorter oligonucleotides are easier to synthesize, Marshall *et al.* discloses that "phosphorodithioate analogs of reduced length represent a more feasible class of potential therapeutic oligonucleotides" (page 6268, last paragraph of the second column). Thus Marshall *et al.* teaches away of the present application which is encompassing oligonucleotides of at least 30 nucleotides in length. In addition, claim 1 of the present invention was amended to claim oligonucleotides of

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at least 30 nucleotides in length. Nowhere in Marshall *et al.*, Matsukura *et al.* and Mergny *et al.* it is taught or suggested a method for the prophylaxis or treatment of a HIV infection in a subject, comprising administering to a subject in need of such treatment a therapeutically effective amount of at least one pharmacologically acceptable oligonucleotide at least 30 nucleotides in length, wherein said oligonucleotide have an anti-HIV activity and wherein the anti-HIV activity of said oligonucleotide occurs principally by a sequence independent mode of action. One skilled in the art having considered Marshall *et al.*, would not be motivated to increase the length of the oligonucleotides to be tested, despite the allegation of the Examiner, as the person skilled in the art is aware of problems of administration and costs related to increasing the length of any oligonucleotides. Thus, in view of the arguments presented hereinabove, Reconsideration of the Examiner's rejections is respectfully requested.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 1, 2, 14-20 and 26-32 at an early date is solicited.

No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

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In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully,

Date: June 8, 2006

By: _____

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Christian Cawthorn
Name of person signing certification

_____ June 8, 2006
Signature Date